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Neuropathogenesis of HAND: Roles for immune activation, HIV blipping, and viral tropism

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Abstract

Purpose of review—To discuss why HIV-associated neurocognitive disorders (HAND) persist despite apparently effective HIV suppression by highly active antiretroviral therapy (ART).

Recent findings—As many as 50% of HIV-infected individuals suffer from HAND despite ART suppression of HIV replication to apparently undetectable levels in most treated individuals. Prior to ART, HIV-associated dementia (HAD), the severest form of HAND, affected ~20% of infected individuals; HAD now affects only ~2% of ART-treated persons, while less severe HAND forms persist. Recent studies link persistent immune activation, inflammation, and viral escape/blipping in ART-treated individuals, as well as co-morbid conditions, to HIV disease progression and increased HAND risk. Despite sustained HIV suppression in most ART-treated individuals, indicated by routine plasma monitoring and occasional CSF monitoring, ‘blips’ of HIV replication are often detected with more frequent monitoring, thus challenging the concept of viral suppression. Although the causes of HIV blipping are unclear, CSF HIV blipping associates with neuroinflammation and, possibly, CNS injury. The current theory that macrophage-tropic HIV strains within the CNS predominate in driving HAND and these associated factors is now also challenged.

Summary—Protection of the CNS by ART is incomplete, probably due to combined effects of incomplete HIV suppression, persistent immune activation, and host co-morbidity factors. Adjunctive therapies to ART are necessary for more effective protection.

Keywords

HAND; HIV; brain; viral blip; HIV blip; inflammation

Introduction

HIV-associated Neurocognitive Disorders (HAND) remain prevalent despite apparently effective suppression of HIV replication by ART in most treated individuals [1**,2**,3**]. The underlying neuropathological processes in the brain that contribute to neurological

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dysfunction in HAND in the era of ART are probably significantly attenuated by such therapy, resulting in a more protracted and less severe clinical course of HAND. Although fulminant encephalitis is now distinctly uncommon in HIV infection, CSF biomarkers of neuroinflammation and brain neuroimaging biomarkers of glial activation and neuronal injury are frequently detected in virally-suppressed individuals. Partial protection against HAND by ART confirms a direct and possibly incomplete link to HIV replication; however longitudinal studies in ART-experienced cohorts indicate surprisingly frequent episodes of CNS viral escape (HIV blipping) in those thought to have complete viral suppression. This suggests a persistent link between CNS HIV replication, immune activation, inflammation and neurological dysfunction that escapes full suppression by current ART. This review will discuss recent studies that investigate these links and identify several gaps in our understanding of HAND neuropathogenesis, including the roles for chronic inflammation, viral blipping, and macrophage-tropic HIV strains within the CNS. Contributing HAND co-morbidity factors are discussed in other reviews in this issue and in several other recent reviews [4*,5*].

CNS HIV infection, persistent immune activation, inflammation and HAND

Early brain infection by HIV is a consistent consequence of systemic HIV infection [6] and CSF HIV RNA levels correlate with severity of neurocognitive dysfunction in ART-naïve subjects, thus linking CNS dysfunction to CNS HIV replication in those individuals (reviewed in [1**,4*]). Perivascular macrophages are the major CNS site of productive HIV replication, although endogenous brain microglia and astrocytes (up to ~15% infection rate) can also harbor virus [7*]. Associated with both early and chronic brain infection is amplification of pro-inflammatory cascades, production of reactive oxygen species, expression of HIV proteins, oxidative stress, and increased production of glutamate and other excitotoxins, all of which have been linked directly or indirectly to neuronal injury and dysfunction [8*]. These links were strongly established in the pre-ART era, but the validity of these links in individuals on suppressive ART is now being challenged, as detection of CSF HIV RNA is more rare and often not correlated with neurocognitive dysfunction in those individuals (reviewed in [2**]). However, there is no credible evidence that ART can irreversibly suppress or clear HIV from or within the CNS. Furthermore, interruption of ART can be associated with viral rebound in the CSF, neuronal injury, and worsened neurocognitive performance [9–11]. With recent studies confirming surprisingly high rates of CSF viral escape (blipping) in individuals felt to be in a state of HIV suppression, a role for persistent CNS HIV infection and replication, even if intermittent, in HAND pathogenesis in ART-experienced patients appears likely [12**]. Equally likely is an association of HIV blipping with immune activation.

Chronic immune activation in HIV infection results in part from increased microbial translocation across a damaged gastrointestinal tract, which shows depletion of gut-associated lymphoid tissue and other structural changes (reviewed in [13**]). Exposure of circulating PBMC to these translocated microbial products, including LPS results in monocyte activation, which is indicated by elevated blood levels of soluble CD14 (sCD14), sCD163, and monocyte-associated CD14 and CD16 [14*]. Notably, elevated levels of circulating CD16+ monocytes, CD14+ monocyte HIV DNA content, sCD14, and sCD163

associated with microbial translocation correlate with an increased risk for HAND [15*], indicating a central role for monocyte activation in pathogenesis. Recent studies have presented a provocative microbial translocation hypothesis: the damaged gastrointestinal tract in HIV-infected individuals harbors more pathogenic microbial populations than that of non-infected individuals [16**]. Therefore, based on accumulating evidence for associations between the gut microbiome and nervous system disorders such as multiple sclerosis and Guillain Barre disease [17**], it is interesting to speculate that certain gut microbiomes could associate with CNS disease progression in HIV infection. This will certainly be a key question for future investigations, and the gut microbiome may ultimately represent another targetable 'host factor' for HAND prevention.

In summary, even in ART-treated individuals with excellent viral suppression the persistence of immune activation, particularly monocyte/macrophage activation in the systemic circulation and CSF correlates with an increased risk for HAND. The pathophysiological factors responsible for establishing and maintaining a state of immune activation are important considerations for HAND prevention strategies.

HIV 'blipping' as a neuroinflammation-associated risk factor for HAND

HIV 'blips' are thought to represent new rounds of HIV replication that result in increased VL above the established lowest level of quantifiable HIV RNA. Viral (HIV) blips are defined as spontaneous expression of viral RNA copies (plasma, CSF) in individuals on ART with sustained antecedent undetectable VLs with return to undetectable levels [18]. CSF discordant blipping is generally defined as a higher RNA copy level of 0.5 log in the CSF in comparison with plasma. An overall plasma HIV blip (> 50 HIV RNA copies/ml) frequency of ~25% has been demonstrated in an observational cohort study (n=3550 virally suppressed patients) [18]. Several causes of blipping are proposed, including differences in VL assay sensitivity [19] and factors affecting HIV replication (ART adherence, immune activation, viral resistance, among others) [18,20*,21]. A role for blips in contributing to increased immune activation and accelerated disease progression has been suggested [20*] although this has been challenged [22].

The significance of viral blips remains undetermined, and their possible association with HAND is under increasing investigation [21*,23,24]. Emerging evidence supports a role for blipping in promoting increased immune activation in the systemic circulation and CNS compartment, which is linked with development of HAND. A link between plasma HIV blips and systemic immune activation has recently been demonstrated in a prospective study of matched blippers and non-blippers [25**]. The study involved 82 individuals with plasma viral blips (VL > 50 and <1000 copies/ml after at least 180 days at undetectable VL on ART) matched with 82 cohort controls without blips. The patients with plasma viral blips after suppressive ART showed increased T cell activation (CD3+HLA-DR+ T lymphocyte level) compared with patients without blips. This suggests that plasma blips might identify those patients at increased risk for immune activation associated with disease progression. Additionally, Castro et al [20*] retrospectively analyzed responses in a cART interruption study and found that subjects with plasma blips above 200 copies/ml prior to cART interruption had lower CD4+ T cell levels under cART, and poorer CD4+ T cell recovery

and increased expression of immune activation markers after cART interruption. This study provided evidence not only that blipping could drive immune activation, but also that the magnitude of the blip can determine future virological failure.

Evidence suggesting that blips might merely maintain an established state of immune activation rather than increase immune activation has also been presented. Benmarzouk-Hidalgo et al [22] studied patients who were switched to simplification treatment of darunavir/ritonavir monotherapy for 24 months after a 6 month period of sustained HIV suppression with combination ART. Outcome groups were assigned as those with continuous aviremia, blips (one plasma VL > 50 copies/ml, preceded and followed by undetectable VL) and intermittent viremia (episodes of VL > 20 copies/ml without blips or failure). Virological failure was defined as two consecutive VL > 200 copies/ml. Only virological failure and not blipping or intermittent viremia was associated with increased immune activation (CD4+ and CD8+ T lymphocyte activation, primarily T_{CM} CD4+ T lymphocytes) from the baseline status. In addition, monocyte activation (plasma sCD14 levels) remained unchanged in the blipping and intermittent viremia groups, while decreasing in the aviremic group. Thus, sustained aviremia associated with significant decreases in activation of CD4+ and CD8+ T lymphocytes and monocytes while virological failure associated with increases in activation of each T lymphocyte subset. Those individuals with blipping and intermittent viremia maintained their previous levels of immune activation. These studies add to the growing evidence indicates that suppression of viral blipping could help in controlling and/or suppressing immune activation in many HIV-infected individuals and they support the importance of determining these associations in the CNS.

Defining the possible associations between blipping in the CNS compartment and increased risk for HAND is critical; HAND persists in HIV-suppressed populations and blipping is surprisingly common in such populations [18,26]. A study of 200 HIV-infected individuals with sustained HIV suppression (median 48 months; range 3.2–136.6) found an overall prevalence of HAND of 69% including a 19% prevalence of significant functional neurological impairment (17% MND, 2% HAD) [27]. Although not designed to detect viral blips, this study suggests persistence of neurological dysfunction in individuals considered to be appropriately treated (HIV suppression) with ART. Given the prevalence of blips in other studies, it raises the question of whether plasma and/or CSF viral blips might contribute to this risk for HAND in suppressed populations.

Recently published and ongoing, unpublished studies directly address the relationships between CSF HIV blipping, inflammation and HAND risk. Eden et al [23] found that ~10% of 69 neurologically normal, HIV ‘suppressed’ patients had detectable CSF HIV RNA, consistent with ongoing HIV replication in the CNS compartment. Furthermore those with detectable CSF RNA had significantly higher CSF expression of markers of monocyte activation (neopterin) and also a longer duration of ART treatment. Follow up studies have indicated that the elevated CSF neopterin levels are not associated with neuronal injury (elevated CSF neurofilament (NFL) levels) at the time of sampling (Figure 1), but whether these blips will associate with future risk for neuronal injury remains to be determined [28*]

Because blips can associate with increased duration of ART and the emergence of ART resistance [23,29], determining the frequency of ART resistance mutations in blippers is critical for ART management of HAND risk. Canestri et al [21] found ART resistance mutations in 7 of 8 CSF specimens from CSF blippers in a small group (n=11) of HIV suppressed (~18 months) patients with neurological symptoms. Ten of the patients had CSF pleocytosis, indicating a strong association between CSF blipping and inflammation. Notably, however, the patients were not evaluated by HAND criteria and so the relationship to HAND is speculative. Additional evidence for emergence of ART resistance in CSF blippers is provided by the ongoing UK PARTITION STUDY of CNS ART penetration [30*]. Three of three CSF specimens tested from a cohort of 38 CSF blippers showed reverse transcriptase resistance mutations, which supports the earlier demonstration and previous reports of a high prevalence of drug resistance in CSF blippers [12**]. Prospective monitoring for drug resistance in the CSF is necessary to determine the risk for developing HAND.

In summary, the argument for a causal relationship between HIV blips, increased immune activation and risk for disease progression in both systemic and CNS compartments is increasing in strength. A role for intermittent HIV replication within the CNS in HAND pathogenesis in virally 'suppressed' ART-experienced patients appears likely. As average ART duration increases, the risks of recurrent blipping will likely become more apparent, and the challenges of monitoring blipping in the CSF as well as plasma will need to be resolved.

CNS HIV tropism, adaptation, and HAND risk: challenging conventional thinking

Establishing a CNS HIV reservoir within the macrophage and microglial lineages by macrophage-tropic (M-tropic) strains, conventionally defined as those that infect both T lymphocytes and macrophages, has been considered a necessary, but not sufficient precursor to the development of HAND. The detection of CSF HIV blipping independent from that detected in plasma is assumed to reflect transient activation of HIV replication of M-tropic strains from these CNS cellular reservoirs. Individuals with the severest form of HAND, HIV-associated dementia (HAD) often have genetically distinct M-tropic variants in their CSF that are not found in the plasma [31], consistent with a central role for replication of M-tropic strains within the CNS in the pathogenesis of HAND.

However, recent evidence also suggests that not only M-tropic strains but also 'T cell-tropic' strains, conventionally defined as those that infect T lymphocytes but not macrophages, can be isolated from the CNS and that each contributes to the development of HAD [31]. Schnell et al [31] found genetically compartmentalized T cell- and M-tropic HIV populations within the CSF that were distinct from those found in the plasma of eight of eight subjects with neurocognitive dysfunction (seven HAD, one milder dysfunction). Three subjects had compartmentalized T cell-tropic populations and five had compartmentalized M-tropic populations. This study challenged the established hypothesis that M-tropic strains are primarily responsible for driving the pathogenesis of HAND.

More recently, the same group further analyzed genetic and phenotypic characteristics cloned *env* sequences of paired CSF/plasma isolates from five individuals and confirmed that CSF-derived viruses segregated into two distinct groups: M-tropic and T cell tropic and, based upon their relative ability to infect cell lines engineered to express tightly-controlled low- and high-level CD4 surface expression respectively [32*]. This well-defined segregation of naturally-occurring HIV phenotypes does not strictly predict the conventional M-tropic and T cell-tropic infection patterns in primary monocyte-derived macrophages or primary CD4+ T lymphocytes. Furthermore, how this phenotype segregation might apply to infection of CD4-negative cell types, such as astrocytes, is unanswered. Thus, the issue of the distribution of HIV strains within different cell lineages/reservoirs within the CNS and the relevance of each to HAND neuropathogenesis has been re-opened. This is particularly relevant to persistence of HIV within the CNS in ART-suppressed patients, the genesis of CSF HIV blips linked to neuroinflammation, and for consideration of CNS HIV eradication strategies.

Finally, studies of CNS HIV compartmentalization have focused almost exclusively on adults with HIV subtype B infection, until recently. A particularly noteworthy study of young Malawian children (n=43) with vertically-acquired HIV subtype C showed that such compartmentalization occurs in up to 50% of children reaching age three [33]. This pertained to *env* evolution of early T cell-tropic strains within the CNS to later M-tropism or through CNS sequestration of a transmitted M-tropic variant from the mother. Notably, the M-tropic compartmentalized strains appeared after 18 months of age and were associated with higher relative CSF viral loads; this suggests growth in macrophages and/or microglia. It also further supports the importance of determining the phenotype/genotype characteristics of viral species in those individuals experiencing CSF HIV blips to identify likely reservoirs accounting for those blips.

Thus, our understanding of the role for HIV tropism in determining early events leading to CNS invasion, establishment of viral reservoirs, and long-term selection pressures within the CNS continues to evolve. We are re-examining our long-held belief that macrophage tropism is the *predominant* HIV determinant of neurovirulence driving HAND, although it appears certain that it is a common factor in HIV neuropathogenesis. Nonetheless, HIV neuropathogenesis might not be an exclusive function of M-tropic strains, and the importance of thoroughly evaluating early events and the role of T cell tropism in CNS infection in both adults and children/neonates is critical for optimizing treatment strategies and achieving better neuroprotection.

Conclusions

HIV associated neurocognitive disorders have persisted despite the effectiveness of ART in limiting HIV disease progression. Strong evidence now links persistent immune activation resulting from microbial translocation with systemic disease progression, and emerging evidence suggests a similar link to HAND. Suppressing this immune activation in both systemic and CNS compartments appears likely to limit disease progression beyond that limited by ART. Nonetheless, HIV suppression is incomplete in a disturbingly high proportion of ART-treated individuals, as estimated by a ~25% overall rate of plasma HIV

blipping. Improvements in ART regimens (and certainly other contributing factors) and patient monitoring can probably reduce this failure rate and limit both systemic and CNS disease progression. Finally, we must more fully understand the phenotypes and tropism of HIV strains entering the CNS and establishing reservoirs. An exclusive role for macrophage-tropic strains has been challenged and this must be addressed, as tropism largely determines HIV cellular reservoirs. This might be the most challenging obstacle to optimizing protection against HAND, in comparison to the challenges of chronic immune activation and plasma/CSF blipping, which can more directly be currently addressed.

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Key Points

- Emerging evidence suggests a link between the persistence of systemic and CNS immune activation and the persistence of HAND in ART-treated individuals.
- HIV suppression is incomplete in ~25% of ART-treated individuals and such plasma HIV blipping might identify those patients at increased risk for immune activation associated with disease progression and future virologic failure.
- Approximately 10% of HIV ‘suppressed’ patients show evidence of ongoing, intermittent CNS replication that associates with increased markers of neuroinflammation
- Both M-tropic and T-cell tropic HIV might play a role in CNS invasion and establishment of CNS viral reservoirs that can lead to HAND.

Figure 1. Hypothetical time course of CSF viral blips, neuroinflammation, and neuronal injury
 Diagram outlining the postulated temporal associations between CSF HIV viral blips, neuroinflammation (CSF neopterin), and neuronal injury (CSF neurofilament light chain, NFL).